PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PV/452/PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CZ2005/000024	International filing date *(day/month/year)* 28.02.2005	Priority date *(day/month/year)* 26.02.2004
International Patent Classification (IPC) or national classification and IPC INV. C07F9/58 A61K31/663 A61P19/00		
Applicant ZENTIVA, A.S. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.09.2005	24.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Seitner, I Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2005/000024

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-27 as originally filed

   Drawings, Sheets

   1-9 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2005/000024

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01/56983 A (THE PROCTER & GAMBLE COMPANY) 9 August 2001 (2001-08-09)

D2: WO 98/57967 A (DONG-A PHARMACEUTICAL CO., LTD; CHA, BONG-JIN; OH, JUN-GYO; KIM, SU-EO) 23 December 1998 (1998-12-23)

D3: MEHTA S C: "ISSUES AND APPROACHES FOR IMPROVING THE SOLUBILITY AND BIOAVAILABILITY OF POORLY WATER SOLUBLE COMPOUNDS" BULLETIN TECHNIQUE GATTEFOSSE REPORT, GATTEFOSSE, SAINT-PRIEST,, FR, vol. 91, no. 91, 1998, pages 65-72, XP008034161 ISSN: 1149-0306

V.1. Novelty:

The present application relates to amorphous forms of Risedronic acid monosodium salt which has not been disclosed in the available prior art.

Consequently, the subject-matter of claims 1-27 is new in the sense of Article 33(2) PCT.

V.2. Inventive step:

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses Risedronic acid monosodium salt in crystalline form.

The subject-matter of claim 1 therefore differs from D1 in that the Risedronic acid monosodium salt is in amorphous form.

The problem to be solved by the present invention may therefore be regarded as the

provision of a further form of Risedronic acid.

The skilled person is aware of the existence of crystalline and amorphous forms and it is considered an ordinary practice to prepare different forms of active ingredients.

The Applicant provides comparative tests showing a better solubility of the amorphous form when compared to the crystalline form.

In general, it is known that amorphous forms of a drug represent the highest energy forms and are therefore used to improve the solubility/dissolution rates of insoluble drugs (see D2 and D3). Consequently, this effect cannot be regarded as unexpected.

Applicant argues that sodium risedronate, as salt of a weaker acid, converts in the environment of gastric juice, which contains HCl, to the more poorly soluble risedronic acid. In comparative tests, Applicant convincingly demonstrated that, in the case of amorphous risedronate, risedronic acid remains in the solution, while in the case of crystalline risedronate, it precipitates within a few seconds.

This effect can indeed be regarded as an unexpected effect which is associated with the novel feature over the prior art.

Therefore, the subject-matter of claims 1-27 can be considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of bone diseases and the subject matter of claims 1-27 is therefore considered as industrially applicable (Article 33(4) PCT).